UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

GENENTECH, INC., Plaintiff, v. THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA, a Pennsylvania non-profit corporation, Defendant.	Case No.: 10-CV-02037-LHK ORDER CONSTRUING DISPUTED CLAIM TERMS OF U.S. PATENT NO. 6,733,752

Plaintiff Genentech, Inc. (Genentech) brings this suit against defendant Trustees of the University of Pennsylvania (U Penn) for a declaratory judgment of non-infringement and invalidity of U.S. Patent No. 6,733,752 (the '752 Patent). By counterclaim, U Penn asserts infringement by Genentech. The parties seek construction of claim terms in the '752 Patent. The Court held a tutorial on March 28, 2011, and a claim construction hearing on April 4, 2011. The Court has reviewed the claims, specification, prosecution history, and other relevant evidence, and considered the briefing and arguments of the parties. It now construes the terms at issue.

I. Background

The invention claimed in the '752 Patent is directed to a method for preventing development of tumors in individuals at risk of tumor development using antibodies. The '752 Patent describes antibodies to the protein expressed by the *neu* oncogene. '752 Patent 1:34-39. The *neu* oncogene codes for a cell surface receptor protein named p185. *Id*. Amplification of the

neu oncogene (and resulting over-expression of p185) have been linked to certain types of cancers, including breast cancer. '752 Patent 1:40-53; 2:45-55. The '752 Patent describes a method for preventing transformation of a breast cell which over-expresses p185 into a cancer cell by treatment with anti-p185 antibodies. These antibodies specifically bind to p185 on the cell surface, and thereby "interfer[e]" with the transformation of the cell into a cancer cell. '752 Patent 2:32-38.

In Example 1, the '752 inventors describe production of anti-p185 mouse antibodies. '752 Patent 4:51-6:60. One of the resulting antibodies was named 7.16.4. *Id.* Cells producing this antibody were deposited in the American Type Culture Collection (ATCC) as accession number HB 10493. *Id.* In Example 2, the inventors of the '752 Patent describe an experiment using transgenic mice that over-express a rat *neu* oncogene ("Bouchard" mice). '752 Patent: 6:62-7:14. The Bouchard mice develop breast tumors at about 40 weeks of age. *Id.* The inventors treated the Bouchard mice with low and high doses of the 7.16.4 antibodies, and reported that the high dose of antibody suppressed tumor formation in half the mice. '752:7:65-8:12.

The parties dispute the meaning of claim terms in independent claim 1 and dependent claims 2, 3, 6, and 7. These claims are reproduced below with the disputed language in bold:

> 1. A method of inhibiting development into **breast cancer cells** of **breast cells that overexpress p185** in **an individual in need of such inhibition** which comprises administering to said individual an antibody which competes with an antibody produced by cell line ATCC Deposit No. 10493 for binding to p185 and specifically binds to p185 in sufficient amount to **down regulate the overexpressed p185** and **inhibit the development of said breast cells that overexpress p185 into breast cancer cells**.
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> 2. The method of claim 1 wherein the antibody has **the complementarity determining regions from an antibody produced by a cell line ATCC Deposit No. HB10493.**
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> 3. The method of claim 1 wherein the antibody has **the variable regions from an antibody produced by a cell line ATCC Deposit No. HB 10493.**
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> 6. The method of claim 5 wherein the antibody is a humanized antibody **with complementarity determining regions from the antibody produced by ATCC Deposit No. HB10493.**
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> 7. The method of claim 5 wherein the antibody is a humanized antibody **with variable regions from the antibody produced by ATCC Deposit No. HB10493.**

II. Legal Standard

Claim construction is a question of law to be determined by the Court. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995). "Ultimately, the interpretation to be

given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (internal citation and quotation omitted).

Claim terms are generally construed to mean what a person of ordinary skill in the art at the time of the invention would have understood them to mean. *Phillips*, 415 F.3d at 1313. When the meaning of a claim term, as understood by persons of ordinary skill in the art, is not immediately apparent, courts are to look to sources available to the public to determine what the disputed claim language means. *Id*. at 1314. These sources include "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id*. (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)).

The Court thus begins by looking at the words of the claims themselves. *Vitronics Corp. v. Conceptronic*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The Court may consider the claim terms and the context in which they are used, including the language of other claims of the patent, both asserted and unasserted. These other claims may help define a disputed claim term because claim terms are normally used consistently throughout a patent, and the usage of a term in one claim may illuminate the meaning of the same term in another claim. Differences between claims may also be a useful guide in understanding the meaning of the particular claim terms at issue. *Phillips*, 415 F.3d at 1314.

Consideration of the specification is also essential. "The specification is . . . the primary basis for construing the claims." *Phillips*, 415 F.3d at 1315. As recognized by the Federal Circuit:

> The specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs. In other cases, the specification may reveal an intentional disclaimer, or disavowal, of claim scope by the inventor. In that instance as well, the inventor has dictated the correct claim scope, and the inventor's intention, as expressed in the specification, is regarded as dispositive.
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> *Id.* at 1316 (internal citations omitted).

Similarly, the court should consider the patent's prosecution history. This may provide evidence of how the PTO and the inventor understood the patent. In addition, the prosecution history may "inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Id.* at 1317 (internal citations omitted). However, because the prosecution history reflects an ongoing negotiation between the patentee and the PTO, it is often difficult to determine precisely the scope or meaning of isolated statements. *Phillips*, 415 F.3d at 1317. Therefore, the prosecution history is generally given less weight than the claims and the specification.

Finally, the court may consider extrinsic evidence, such as dictionaries or technical treatises, if such sources are helpful to determine the "true meaning" of claim terms. *Phillips*, 415 F.3d at 1318, quoting *Markman*, 52 F.3d at 980. While extrinsic evidence may aid claim construction, it cannot be used to contradict the plain and ordinary meaning of a claim term as defined within the intrinsic record. *Phillips*, 415 F.3d at 1322-23.

With these principles in mind, the Court turns to the disputed claim terms.

III. Analysis

A. "Breast cancer cells"

U Penn argues that "breast cancer cells" are "cells, the origin of which is breast tissue, that have the properties of uncontrolled growth and invasiveness." Genentech argues that this term means "cells from the breast that (a) have malignant form and structure and the potential to invade and metastasize or (b) have invaded or metastasized." The parties agree that there is no explicit definition of "breast cancer cells" in the patent. The parties likewise agree that as cells develop into cancer, they accumulate changes over time: from a normal cell exhibiting no cancerous attributes, to a cell exhibiting some abnormality (such as over-expression of p185), to a cell that divides to form a tumor but cannot yet invade surrounding tissue, to a cell that has gained the ability to invade surrounding tissue, and finally, to a cell that can leave the site of invasion and metastasize to remote parts of the body. U Penn's expert expressed this as "a multi-step theory of

progression to a cancerous state." Corrected Schlissel Decl. at ¶ 30. The parties further agree that tumor cells which have developed the ability to invade or metastasize are cancer cells.

The parties' disagreement is in identifying the earliest point in the progression towards becoming a cancer cell that a cell can be considered breast cancer. The construction of this term will determine what cells the patented method acts upon to prevent their development into breast cancer. U Penn argues that the "breast cancer cells" which the patented method inhibits are cells which can not only divide to form tumors but can also invade. Therefore, U Penn's construction would encompass treatment of cells that have already formed tumors, but are not yet invasive. Genentech argues that "breast cancer cells" is a more inclusive term, covering cells that have undergone certain morphological changes but which may only have the *potential* to invade other tissues—meaning that they must undergo further changes before they have the present ability to invade (or to metastasize).

In support of its argument, U Penn relies primarily on extrinsic evidence of definitions of "cancer." U Penn cites two textbooks from near or before the presumptive priority date of the '752 Patent (March 30, 1994).[1] First, *Molecular Cell Biology*, which states that:

> [T]o become a cancer cell, a normal cell undergoes many significant changes. It continues to multiply when normal cells would be quiescent; it invades surrounding tissues, often breaking through the basal laminas that define the boundaries of tissues; and it spreads through the body and sets up secondary areas of growth in a process called metastasis."
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> James E. Darnell *et al*., *Molecular Cell Biology*, 1288 (3d ed. 1995).

U Penn also cites *Cell and Molecular Biology*, which states that:

> Cancer cells are characterized by an *uncontrolled cell growth, invasion of other tissues*, and *dissemination* to other sites of the organism producing secondary tumors.
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> E.D. P. De Robertis & E.M.F. De Robertis Jr., *Cell and Molecular Biology*, 147 (8th ed. 1987).

U Penn argues that these definitions were known by those having skill in the art in 1994, and that the specification reflects this understanding of what cancer is. U Penn cites the use of the word "malignant" in the specification, arguing based on another extrinsic source that "malignancy"

[1] The '752 patent claims priority to a Patent Cooperation Treaty (PCT) application, number 08/525,800, filed March 30, 1994.

is "the essential property of cancer cells that is demonstrated by their ability to proliferate indefinitely [and] to invade surrounding tissues." Richard P. Hill and Ian F. Tannock, *Introduction* to *The Basic Science of Oncology*, at 2 (Ian F. Tannock & Richard P. Hill, eds., 2d ed. 1992). Thus, U Penn argues, when the patentees discussed "prevent[ing] cells from becoming malignant" while prosecuting the patent, they meant preventing cells from developing the abilities to divide indefinitely *and* to invade other tissue.

While the specification refers to "malignancy," it appears to use this word simply to mean "tumor formation." In the discussion of the Bouchard mouse experiments, the inventors note that "[n]early half of the mice in both control groups and in the low dosage groups developed two to five independent tumors within a six week period after the first tumor became visible. In contrast, *all animals that developed malignancy in the high dosage group had only a single tumor*. The tumor volume of the high dosage group at a given point after tumor appearance was always smaller than that of control mice at the same point." '752 Patent 8:4-12 (emphasis added). Thus, the patent equates "malignancy" simply with "tumor presence." While the patent also uses "[i]ncreased stage of malignancy" to describe later stages of cancer "characterized by large tumor size and increased number of positive lymph nodes [indicating invasion]," it does not say that the tumors observed in the Bouchard mice all exhibited increased malignancy. '752 Patent 1:45-49. In fact, the inventors note that the "malignancy" observed in the high dosage group mice showed *decreased* tumor size in comparison to the control mice, as cited above. Decreased tumor size is the opposite of what one would expect with increased malignancy as it is defined in the patent.

U Penn also relies on the "Tannock and Hill" reference cited during prosecution of the '752 Patent for intrinsic support for its definition. On April 10, 2002, the examiner rejected the pending claims drawn to "inhibiting stochastic development of tumors that overexpress p185." The examiner rejected the claims, finding that "[t]he specification does not disclose a method for inhibiting tumorigenesis of 'a cell that overexpresses p185' into 'a fully developed tumor cell . . . .'" April 10, 2002 Office Action at 4. On Oct. 10, 2002, U Penn responded to this argument, stating that "as of the filing date of the application, it was well accepted . . . that many tumors show a tendency toward increasing malignancy with time, from 'benign [i.e., non-tumor tissue] to non-

invasive but premalignant lesion to frank malignancy." Oct. 10, 2002 Amendment at 4-5. In support, U Penn cited a reference, *The Basic Science of Oncology*, which was attached to the Amendment. This reference illustrates the principle of increasing malignancy with the example of cervical cancer, stating that "[i]n some tumors there is an orderly progression from benign tissue to noninvasive but premalignant lesions (e.g., carcinoma in situ of the cervix) to frank malignancy." *The Basic Science of Oncology* 144 (Ian F. Tannock and Richard P. Hill, eds.) (2d ed. 1992). U Penn argues that this reference was introduced "so that the Patent Office would understand the distinction the patent makes between malignant and pre-malignant cells," and that this reference is intrinsic evidence supporting its construction. U Penn Reply Re Claim Construction (Dkt. No. 156) (Reply) at 6.

Genentech argues that "breast cancer cells" should be defined using the tools a medical professional would use to diagnose cancer. Citing the paper which introduced the Bouchard mice (incorporated by reference into the '752 Patent specification), Genentech argues that breast cancer cells are characterized and identified by their "malignant form and structure." '752 Patent 8:13-16 (citing Louise Bouchard et al., *Stochastic Appearance of Mammary Tumors in Transgenic Mice carrying the MMTV/c-neu Oncogene,* in *Cell*, Vol. 57, 931-36 (1989) (Bouchard paper). Genentech's expert, Dr. Cote, identified four elements of "malignant form and structure" used to characterize the tumors in the Bouchard mice: (1) high nucleus-to-cytoplasm ratio; (2) a darker color when stained (hyperchromasia); (3) a nucleus of irregular size or shape; (4) disorganized cell growth. *See* Cote Decl. ¶ 31. Genentech notes that in the Bouchard paper, the authors analyzed the four elements listed above via microscope and concluded that the mouse tumors were "an adequate model for human breast cancers overexpressing *c-neu*." Bouchard paper at 1. The '752 Patent specification cites the Bouchard paper as evidence that the mouse tumors have "been previously characterized in detail." Dr. Schlissel agreed that the four elements identified by Dr. Cote are "among the criteria pathologists would use in attempting to diagnose whether a tissue sample is from a cancer or not." Ramani Decl., Ex. 2 (Schlissel Dep.), 182:7-10.

In the '752 Patent, the inventors identified the reduction of tumors in the Bouchard mice as proof that the patented method works. They stated that "6 of 12 mice in [the high dose treatment]

group (50%) remained free of tumors at more than 90 weeks of age. This indicates that treatment of transgenic mice with . . . 7.16.4 . . . twice weekly can effectively suppress tumor development in a large fraction of these mice for almost their entire lifespan." '752 Patent 7:65-8:4. The '752 Patent does not distinguish between suppression of invasive and non-invasive tumors; it simply states that the patented invention can "suppress tumor development," resulting in tumor-free mice. *Id*. U Penn argues that the tumors of the Bouchard mice "were not pre-invasive," but in Figure 3, the Bouchard paper shows both invasive and non-invasive tumors and labels them all "mammary tumors." Reply at 7. In addition, at the claim construction hearing, U Penn stated that the Bouchard mouse tumors were both non-invasive and invasive. U Penn also argues that the Bouchard mice developed "malignant outgrowth," meaning secondary tumors in the lungs, but this occurred in only three of the five mice tested. In short, it appears that both Bouchard and the inventors counted tumor development as cancer, and tumor absence as non-cancer, without distinguishing between invasive or non-invasive tumors.

Both parties cite evidence that DCIS was categorized as both precancer and cancer at the time of the '752 Patent prosecution as well as today. Although the extrinsic evidence U Penn cites for definitions of the generic term cancer suggests that the term may require the ability to invade when used generally or in other contexts, the claims of the '752 Patent are directed at preventing development of breast cancer. U Penn admits that in the context of breast cancer, non-invasive tumors (*ductal carcinoma in situ*, or DCIS) are "often . . . categorized with cancer" and are sometimes "called . . . noninvasive cancer." Reply at 9. At the claim construction hearing, U Penn relied heavily on the intrinsic Tannock and Hill reference, which describes cervical carcinoma in situ as "noninvasive but premalignant," to demonstrate that carcinoma *in situ* should be considered premalignant and therefore excluded from the definition of cancer. First, this reference is at best ambiguous, since the statement "noninvasive *but* premalignant" suggests that the ordinary presumption is that carcinoma *in situ* is noninvasive and malignant. Furthermore, as Genentech points out, other intrinsic references describe DCIS as cancerous. For example, the Bouchard paper itself cites another reference which refers to "ductal carcinoma in situ" as "breast cancer." van de Vijver et al., *Neu-Protein Overexpression in Breast Cancer*, 319 (19) New Eng. J. Med. 19,

1240 (1988). Genentech also cites extrinsic evidence showing that skilled artists currently use the term "cancer" inconsistently, sometimes referring to DCIS as cancer and other times referring to it as precancer. *See* Reply Ex. P (a pamphlet published by U Penn which states that "'Breast Cancer' is a non-specific term used to describe a whole family of cancers . . . DCIS . . . is a unique form of breast cancer."); Ex. G (a Johns Hopkins University webpage stating that "DCIS is 'noninvasive breast cancer'" but elsewhere stating that DCIS is "precancer").

Ultimately, what U Penn calls "loose terminology" (Reply at 9) associated with the use of "cancer" in the context of breast cancer suggests that if the inventors intended to exclude non-invasive tumors such as DCIS from the meaning of "breast cancer cells," they could have and should have made this distinction clear. Instead, the patent discusses suppression of all tumors without distinguishing between invasive and non-invasive tumors. As discussed above, the patent equates "malignancy" with "tumor presence." *See, e.g.*, '752 Patent 8:4-12. The Court finds that U Penn's construction limits the word "cancer" to only the most advanced forms of invasive tumors without adequate support for doing so.

Therefore, the Court finds that Genentech's proposed definition, which includes non-invasive tumors such as DCIS, is more consistent with the intrinsic evidence than U Penn's definition, which excludes them. In addition, the Court finds that Genentech's proposed elements of "malignant form and structure" are supported by the intrinsic record. Given the incorporation of the Bouchard paper and the nature of the mouse study disclosed in the '752 Patent, it is appropriate to incorporate these diagnostic criteria into the definition of "breast cancer cells." Adopting a construction that can be applied using existing diagnostic tools is consistent with the intrinsic record, which shows that Dr. Bouchard used such tools to determine that her mouse model adequately modeled human breast cancer.

The Court further finds that since the parties agree that cancerous cells divide uncontrollably at least some of the time, it is appropriate to add the ability for uncontrolled growth from U Penn's proposed construction into the construction of "breast cancer cells." Genentech's objection to this limitation is that breast cancers do not grow uncontrollably all the time, and can include cells that "do not grow at all, let alone uncontrollably." Opp'n Br. Re Claim Construction

(Opp'n) at 12. However, the *ability* for uncontrolled growth is what permits a tumor to form, and contributes to the "disorganized cell growth" element of Genentech's "malignant form and structure" criteria.

Accordingly, the Court construes "breast cancer cells" to mean "**cells from the breast that have malignant form and structure, the ability for uncontrolled growth, and the potential or ability to invade or metastasize.**"

B. "Breast cells that overexpress p185"

U Penn argues that this term means "cells, the origin of which is breast tissue, that overexpress p185 and are not breast cancer cells." Genentech argues that this term means "normal cells in the breast that overexpress p185." Thus, the parties agree that these cells are not cancer cells and that they overexpress p185. The dispute centers on whether these cells must be in the breast, and whether they must be "normal" (besides their overexpression of p185).

Genentech argues that the cells in question must be "normal" because the specification repeatedly states that the invention is directed to preventing "normal cells from transforming into tumor cells." '752 Patent 3:11-12. It is true that the specification describes the invention this way. Originally, the claims were drafted to claim methods of preventing "normal" cells from becoming transformed into tumor cells. However, the examiner rejected the claims for treatment of "normal" cells, finding that such claims were not enabled. The examiner reasoned that while the transgenic Bouchard mouse cells which were used in Example 2 overexpressed *neu*, "normal cells do not overexpress the *neu* oncogene." Oct. 4, 2000 Office Action at 5. Therefore, the inventors had not enabled treatment of "normal" cells. *Id.*

U Penn first amended its claims by replacing the word "normal" with "untransformed." Feb. 5, 2001 Response and Amendment at 10. The examiner again rejected the claims as non-enabled, finding that "[t]he specification discloses treating cells that already overexpress *neu* oncogene in transgenic mice . . . [t]he specification however does not teach how to prevent transformation from normal cells to tumor cells . . . ." April 24, 2001 Office Action at 4. In response, U Penn amended the claim again to replace "untransformed cell" with "a cell that overexpresses p185." Aug. 24, 2001 Response and Amendment at 4. The Examiner initially

rejected these claims as non-enabled, on the basis that human cells overexpressing p185 "already are tumor cells," but U Penn traversed this rejection by arguing that in the context of the Bouchard mice (wherein *all* cells overexpress p185), "most cells that overexpress p185 are normal" and "overexpression of p185 can be found in tumor cells or non-tumor cells." April 10, 2002 Office Action at 7; Oct. 10, 2002 Amendment at 7. After some additional amendments, the claims were granted to a method for treating "breast cells that overexpress p185." On the basis of U Penn's arguments to the examiner that p185 overexpressing cells can be otherwise normal, Genentech argues that the Court should read "normal" into this claim term. However, the fact that U Penn had to remove "normal" from the claims in order for them to be granted counsels against re-inserting it. Genentech cites cases holding that when the written description "clearly identifies what [the] intention is," any statement by the patentee during prosecution indicating an intention to broaden the claims is entitled to little weight. *Honeywell Int'l., Inc. v. ITT Indus., Inc.,* 452 F.3d 1312, 1319 (Fed. Cir. 2006). However, the Court finds that the addition of the "p185 overexpressing" limitation was a significant *narrowing* of the claim when compared to a claim for treating any normal cell. Therefore, *Honeywell* is inapposite.

In any case, in light of the Court's construction of "breast cancer cells," it appears that Genentech's concern that this claim could cover cells that overexpress p185, form tumors, and have malignant form and structure is not an issue, because such cells would fall under the definition of "breast cancer cells." Accordingly, the Court declines to add the word "normal" into the definition of this claim term.

Likewise, Genentech's concerns that the limitation "in the breast" must be added to this claim term appear to be resolved by the Court's construction of "breast cancer cells." Genentech argues that a construction without this limitation would theoretically cover non-cancerous, p185-overexpressing breast cells that are outside the breast, but there is no evidence that any such cells exist.[2] While the Court agrees with Genentech that neither party has introduced evidence of non-

[2] At the claim construction hearing, the Court asked U Penn for any intrinsic evidence of non-cancerous, p185-overexpressing breast cells outside the breast. U Penn argued that, in theory, any breast cell in the Bouchard mouse that somehow moved outside the breast by means other than invasion or metastasis would fit this description, since all cells in the Bouchard mice overexpress p185. U Penn has introduced no evidence of a cell in the Bouchard mouse that actually did this,

cancerous p185-overexpressing breast cells that occur outside the breast, the fact that there appear to be no such cells makes the addition of the "in the breast" limitation superfluous. Genentech's concern that this term could cover micrometastases (which it defines as "cancer cells that have spread to distant locations but may not yet be actively proliferating at the secondary site") is resolved because the Court has adopted a definition of "breast cancer cells" which only requires the ability for uncontrolled growth rather than the present characteristic of uncontrolled growth. Therefore, micrometastases are "breast cancer cells" and are thus excluded from "breast cells that overexpress p185."

Accordingly, the Court construes "breast cells that overexpress p185" to mean "**cells, the origin of which is breast tissue, that overexpress p185 and are not breast cancer cells.**"

C. "an individual in need of such inhibition"

U Penn argues that this term means "an individual who (i) has a family history of *neu*-associated breast cancer or a genetic predisposition to *neu*-associated breast cancer but who has not developed *neu*-associated breast cancer; or (ii) has had her/his *neu*-associated breast cancer tumors removed by surgical resection, or has been diagnosed as having *neu*-associated breast cancer enter remission." Genentech argues, in essence, that the term is limited to only the first group in U Penn's construction: "An individual who is predisposed to develop p185-expressing breast cancer cells; not an individual who has had a p185-expressing tumor removed or enter remission."

The claim language itself is limited only by the need for inhibition, and does not explicitly mention either the genetically predisposed or the tumor removed/remission groups. The specification, however, identifies both of U Penn's proposed classes of potential patients as individuals who could benefit from the patented method. Under "Patient Population," it states: "[T]he present invention . . . is particularly useful in high risk individuals who, for example, have a family history of *neu*-associated cancer or show a genetic predisposition . . . [and] is particularly useful to prevent neu-associated tumors in patients who have had neu-associated tumors removed

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however. Moreover, U Penn admits that outside of this hypothetical, there is no other intrinsic evidence indicating that p185-overexpressing breast cells that are not cancerous appear outside the breast.

by surgical resection." '752 Patent: 4:6-16. Therefore, based on the claim language and the specification, there is significant support for U Penn's definition.

However, Genentech argues that the second class of patients in U Penn's construction—those who have had a tumor removed or have had cancer enter remission—should be excluded from the claim based on a prosecution disclaimer. Genentech cites the examiner's rejection of all claims, including pending independent claims 1 and 12, which claimed treatment of "an individual who has had a tumor that is characterized by tumor cells that express p185 removed," and "an individual who has had a tumor that has p185 on its cell surfaces removed or who has had cancer characterized by tumor cells that have p185 on their surfaces enter remission," respectively. *See* Jan. 8, 2002 Amendment at 2. The examiner rejected all pending claims on the basis that the Bouchard mice have "overexpression of p185 in normal mammary glands before the appearance of visible tumors . . . [t]he specification does not disclose[] that said mouse has had a tumor that has p185 on its cell surfaces removed or has had cancer characterized by tumor cells that have p185 on their surfaces enter[] remission." April 10, 2002 Office Action at 4.

U Penn responded to this rejection by attempting to traverse the Examiner's rejection. On October 10, 2002, U Penn submitted a response to the examiner arguing that the specification adequately disclosed treatment of removal and remission patients, because it discloses that "prevention of metastasis or recurrence is feasible by administering anti-p185 antibodies." Oct. 10, 2002 Amendment at 3. U Penn argued that "contrary to the Examiner's position, Applicants have disclosed methods for inhibiting transformation of a cell that overexpresses p185 in an individual who has had a p185-tumor removed or who has had tumor cells characterized by p185 on their surfaces enter remission." *Id.* at 4.

The examiner never responded to this argument in writing. Instead, in June, 2003, U Penn and the examiner had a telephonic conference after which U Penn submitted amended claims. In this amendment, U Penn removed the "tumor . . . removed" limitation from claim 1, and replaced it with the "individual in need of such inhibition" language which was eventually issued. *See* June 19, 2003 Draft Amendment at 2; July 18, 2003 Amendment at 2. In addition, U Penn cancelled claim 12 (the claim drawn to "remission" patients as well as "tumor removed" patients).

The parties dispute how to interpret this history. Genentech argues that U Penn's cancellation of claim 12, and its amendment of claim 1 to remove the specific reference to patients from whom tumors had been removed, indicate that U Penn had to give up the "tumor removed" and "remission" patients from the scope of the claims in order to overcome the examiner's April 10, 2002 written description rejection. Genentech argues that U Penn's "surgical" removal of all references to tumor removal and remission indicate U Penn's "clear disclaimer" of this claim scope. *See* Opp'n at 29. Genentech cites *Rheox, Inc. v. Entact, Inc.*, 276 F.3d 1319, 1326 (Fed. Cir. 2002) in support of its argument. In *Rheox*, the patentee explicitly disclaimed compounds of higher solubility to overcome an anticipation rejection. *Id*. As a result, the patentee was barred from later arguing that the claims should encompass such compounds (even though one of the disclaimed compounds was a preferred embodiment of the invention). *Id*.

U Penn argues that it never clearly disclaimed the "tumor removal" or "remission" patients from the scope of the claims. U Penn notes that it did not respond to the examiner's rejection with an amendment, but instead attempted to traverse the rejection . U Penn also notes that the claim language that was eventually allowed ("individual in need") is, on its face, broader than the amended language in either claim 1 or claim 12 (both of which were limited to tumor-removal and/or remission patients). Unfortunately, the prosecution history provides no insight into the examiner's reasoning in allowing the amended claims, since there is no record of the substance of the telephone conversation preceding the key amendment. Thus, the parties and the Court must rely on inferences and even guesses in order to decipher the import of the July 18, 2003 amendment. Capitalizing on this uncertainty, U Penn cites the Federal Circuit's holding that "[t]here is no 'clear and unmistakable' disclaimer if a prosecution argument is subject to more than one reasonable interpretation, one of which is consistent with a proffered meaning of the disputed term." *Sandisk Corp. v. Memorex Prods., Inc.*, 415 F.3d 1278, 1287 (Fed. Cir. 2005) (citing *Golight, Inc. v. Wal-Mart Stores, Inc.*, 355 F.3d 1327, 1332 (Fed. Cir. 2004). U Penn argues that there has been no such clear disclaimer here, and thus that Genentech's proposed limitation must be rejected.

In light of the requirement that a disclaimer be "clear and unmistakable," the Court finds that U Penn's proffered explanation of the amendment is not unreasonable and is consistent with inclusion of the tumor-removal and remission patients in the scope of the claims. Accordingly, the Court does not find that U Penn disclaimed the tumor-removal/remission patients. Unlike the *Rheox* case, in which the patentee (in direct response to an anticipation rejection) explained that its amendments were made to distinguish the prior art soluble compounds, the record here is far less clear. *Rheox,* 276 F.3d at 1322. The court in *Rheox* relied, in part, on the cancellation of claims to high-solubility compounds as evidence of the disclaimer, and Genentech argues that U Penn's cancellation of claim 12 is similar evidence. *Rheox,* 276 F.3d at 1326. But cancelled claim 12 does not provide such obvious support for a disclaimer. U Penn argues that because claim 1 was amended to claim a broader class of patients (encompassing those originally claimed in claim 12), it was no longer necessary to maintain claim 12 and its dependent claims. In the language of *Sandisk,* this explanation is not unreasonable, and is consistent with U Penn's construction.

As further support for U Penn's argument, U Penn notes that early in the prosecution, it amended the claims to exclude individuals with a genetic predisposition to overexpress p185. It made this amendment to overcome a rejection based on a lack of enablement of such claims. From 1999 until 2003, the claims were limited to treating tumor-removal or remission patients. U Penn argues that there is no more reason to conclude that the genetically predisposed patients were recaptured with the amendment to "individual in need" than there is to conclude that the tumor-removal/remission patients were recaptured, yet both parties agree that at least the former claim scope *was* reclaimed. The Court agrees with U Penn that this history supports the conclusion that the amendment to "individual in need" was intended to be a broadening amendment, including both classes of patients. While such amendments are uncommon, they are possible. *3M Innovative Properties Co. v. Avery Dennison Co.,* 350 F.3d 1365, 1372 (Fed. Cir. 2003).

Accordingly, the Court construes "an individual in need of such inhibition" to mean "**an individual who (i) has a family history of *neu*-associated breast cancer or a genetic predisposition to *neu*-associated breast cancer but who has not developed *neu*-associated breast cancer; or (ii) has had her/his *neu*-associated breast cancer tumors removed by**

surgical resection, or has been diagnosed as having *neu*-associated breast cancer enter remission."

D. "to down regulate the overexpressed p185"

U Penn argues that this term means "to decrease the ability of the overexpressed p185 receptors to participate in their function." Genentech argues that it means "to actively internalize p185 so that the expression of the receptor on the cell surface is reduced." The parties agree that this term is not defined in the specification itself. Genentech argues that during prosecution, U Penn submitted materials defining the term as Genentech proposes. U Penn argues that the term should be construed based on how a skilled artist would define "down regulate," and cites extrinsic evidence in support of its proposal.

The Court does not agree with Genentech that U Penn defined "down regulate" to mean "active . . . internalization" during prosecution. Genentech bases its argument on U Penn's submission of a declaration and article by one of the inventors of the '752 Patent. The declaration was submitted in response to a rejection of the pending claims for lack of enablement. In rejecting the claims, the examiner noted that "many immunotherapeutic agents are inactive in other species . . . one of skill in the art could not extrapolate prevention of tumor development due to neu oncogene in mice to said prevention in human." Oct. 14, 1998 Office Action at 3. In response to this rejection, U Penn submitted a declaration by inventor Greene. Greene stated that "the mechanisms by which the present invention operate[s] are sufficiently well understood to conclude that one skilled in the art would conclude that the claimed invention is enabled by the specification." Feb. 18, 1999 Amendment. Greene attached a review article that he co-authored, titled "Her2/neu: A Receptor Tyrosine Kinase with Developmental and Oncogenic Activity." This article contains a glossary which defines "receptor internalization or downregulation" as "a process that takes place upon ligand binding, in which the receptor that is diffusely distributed on the cell surface undergoes rapid lateral mobility, clusters in coated pits, and become[s] internalized so that the expression of the receptor on the cell surface is reduced." Genentech argues that this submission defined downregulation as a synonym of receptor internalization. Genentech cites

additional articles by the inventors, cited during the prosecution history of the '752 Patent, which it argues similarly define "down regulate" to mean "internalization."

U Penn counters that at the time Greene's declaration was submitted, the pending claims did not contain a "down regulation" limitation. U Penn argues it would be unreasonable to find that the inventors defined a claim term which was not at issue at the time. However, the specification does refer to "down regulation" as the mode of action of the '752 Patent claimed method, so it is not unreasonable to think that U Penn could have defined this term even before a claim was specifically drawn to it. However, the Court finds that the articles in the specification and prosecution history, when viewed as a whole and in the light of the entire prosecution, do not limit "down regulate" to "internalize" as Genentech argues. While some of these articles indicate that internalization of p185 is involved in treatment with the claimed antibodies, they do not state definitively that this is the *only* possible mode of action. For example, one of the papers co-authored by two of the '752 inventors investigated "whether antibody 7.16.4 could remove p185 from the cell surface . . . ." *See* Jeffrey A. Drebin et al., *Down Regulation of an Oncogene Protein Product and Reversion of the Transformed Phenotype by Monoclonal Antibodies*, 41 Cell 695, 696 (1985). While the paper states that the antibody treatment is "not cytotoxic" (cell-killing), the overall focus of the paper is on testing whether p185 is removed from cell surfaces rather than on ruling out other modes of action.

Likewise, another paper cited during prosecution and authored by two of the inventors states that "[o]ur current view of the mechanism by which anti-p185 antibodies directly affects the malignant phenotype involves the oligomerization of the oncogene encoded protein on the cell surface." *See* Jeffrey A. Drebin et al., *Monoclonal Antibodies Reactive with Distinct Domains of the neu Oncogene-encoded p185 Molecule Exert Synergistic Anti-Tumor Effects in Vivo*, 2 Oncogene 273, 275 (1988). This statement suggests that when this paper was published, in 1988, the inventors' understanding of how the antibodies worked was still developing. It does not categorically define "down regulate" to mean only "internalize." Another paper cited during prosecution is a review of "receptor-mediated endocytosis." Though the paper describes internalization of p185 as "down modulation," it does not state that internalization is the *only* way

to down regulate p185. *See* Valerie I. Brown & Mark I. Greene, *Molecular and Cellular Mechanisms of Receptor-Mediated Endocytosis*, 10(6) DNA and Cell Biology 399, 404-05 (1991). Overall, the cited references do not suggest a strict definition of "down regulate." Accordingly, Genentech's construction of this term is too narrow.

In support of its proposed construction, U Penn cites extrinsic evidence from what it calls the "leading treatises on molecular biology" which state that down regulation may proceed by various different means:

> The down regulation of receptors occurs in several ways, including (1) removal of the receptor from the cell surface, (2) alterations to the receptor that lower its affinity for ligand, or (3) alterations to the receptor that render it unable to initiate changes in cellular function.
>
> Down-regulation of cell-surface hormone receptors can occur in several ways. Receptors can be internalized by endocytosis, thus decreasing the number on the cell surface, and then either destroyed or stored in intracellular vesicles. Alternatively, the number of receptors on the cell surface is not decreased but their activity is modified, so that they either cannot bind ligand, or bind ligand but form a receptor-ligand complex that does not induce normal cellular response. Receptors for many hormones are regulated by two or more of these mechanisms.

Wayne M. Becker et al., *The World of the Cell* 754 (3d ed. 1996); *Molecular Cell Biology* at 912; *See* Opening Br. Re Claim Construction (Dkt. No. 112) ("Opening Br.") at 27-28.

U Penn argues that because it was well-known that down-regulation can be achieved through multiple routes, and because the inventors did not specify which mode of down-regulating the patent claimed, it would be improper to limit the term to any one route. Rather, U Penn urges, the Court should simply define the term functionally, as a means of decreasing the function of p185. Genentech objects that this definition is overly broad, and could potentially include killing the cell entirely, which U Penn admits is not down-regulation. *See, e.g.,* Opening Br. at 25 ("ADCC/CDC[3] is not down regulation. The University's construction does not suggest otherwise."). Since both the parties agree that down regulation does not include ADCC/CDC, the Court includes this limitation in the construction of the term to address Genentech's concern.

Because U Penn did not define "down regulate" to mean only "internalize" during prosecution, and because extrinsic evidence shows that it was well known in the art that "down

[3] ADCC stands for "antibody dependent cellular cytotoxicity" and CDC stands for "complement-mediated cytotoxicity." Both processes result in cell death. *See* E.1., below.

regulation" of receptors can proceed through various means, the Court adopts U Penn's construction of this term, with the additional limitation that "down regulate" cannot encompass ADCC/CDC. The Court construes "to down regulate the overexpressed p185" to mean "**to decrease the ability of the overexpressed p185 receptors to participate in their function, by means other than antibody dependent cellular cytotoxicity (ADCC) or complement-mediated cytotoxicity (CDC).**"

E. "inhibiting development into breast cancer"

U Penn argues that this term needs no further construction, in light of the Court's construction of "breast cancer cells." Genentech argues that U Penn disclaimed certain modes of action during prosecution, and that the Court should adopt the following construction to reflect these disclaimers: "preventing breast cells that overexpress p185 from becoming breast cancer cells without (1) using ADCC or CDC, (2) preventing or eliminating metastasis, or (3) enhancing chemotherapy." For the reasons discussed below, the Court does not agree that the proposed limitations were introduced.

1. ADCC/CDC:

ADCC stands for "antibody dependent cellular cytotoxicity" and CDC stands for "complement-dependent" or "complement-mediated cytotoxicity." Both are means by which the immune system kills a target cell. *See generally* Corrected Schlissel Decl., ¶¶ 62-68; Cote Decl. ¶¶ 67-73. Genentech argues that U Penn clearly disclaimed these processes from the patented method during prosecution. U Penn counters that while the patented method does not cover using ADCC/CDC, its statements did not exclude these processes from occurring otherwise when the claimed antibodies are administered.

Early in the prosecution of the '752 Patent, the examiner rejected the claims for a lack of enablement. The examiner's rejection was based on the understanding that immunotherapy results obtained in a mouse model did not translate well to humans. The examiner stated that "[a]lthough the response of animals to chemotherapy, radiation and surgery is generally predictive of their effect in human patients, it is not the case with immunotherapy. Many immunotherapeutic agents are inactive in other species." Dec. 3, 1996 Office Action at 4. In overcoming this rejection, U

Penn responded that not all animal immunotherapeutic studies lacked predictive power in humans. U Penn distinguished the claimed antibodies from other molecules such as "immunomodulators, cytokines, lymphokines and other factors." U Penn distinguished molecules like these from antibodies by arguing that "[t]he present invention does not use ADCC or CDC to prevent transformation of normal cells into tumor cells. Accordingly, there is no reason that the antibody therapy of the invention would not work in humans . . . [t]hose having ordinary skill in the art would accept Applicants' data because antibody activity is fully predictable cross-species provided that no accessory immunological mechanisms (complement mediated cytotoxicity or ADCC) are employed. No such mechanisms are employed in the present invention." May 5, 1997 Amendment at 4-5. Thus, U Penn argued that the Bouchard mouse studies should be considered enabling because the invention does not use CDC or ADCC.

Both U Penn and Genentech agree that the patented method does not cover use of the claimed antibodies resulting in ADCC or CDC. Their disagreement is about whether U Penn's statements "exclude the possibility of ADCC/CDC ever occurring as an additional effect beyond down regulation." Reply at 17. While this is a very close issue, in light of the Federal Circuit's holding in *Sandisk*, the Court agrees with U Penn that its statements about the "present invention" should not be taken as a representation by the inventors that ADCC/CDC could *never* result from administration of the claimed antibodies.

The Court must consult the prosecution history in claim construction, in part, in order to "ensure . . . that claims are not construed one way in order to obtain their allowance and in a different way against accused infringers." *Chimie v. PPG Indus.*, 402 F.3d 1371, 1384 (Fed. Cir. 2005). This is necessary in order to protect "the public's reliance on definitive statements made during prosecution." *Omega Eng'g., Inc. v. Raytek Corp.*, 334 F.3d 1314, 1324 (Fed. Cir. 2003). U Penn argues that while "down regulation" does not include ADCC/CDC, its statements did not exclude the possibility that these processes could occur as an "additional effect" of practicing the patented method. Reply at 17. Therefore, U Penn argues, these statements should not be held as indications to the public that use of antibodies triggering these methods *and* causing down regulation are non-infringing.

In support of its argument, U Penn relies heavily on *Sandisk*, in which the Federal Circuit reversed the trial court's finding of disclaimer. *Sandisk*, 415 F.3d at 1290. The district court focused on statements limiting the "claimed memory system" to partitioned memory, and found that the claims required *every* memory cell in a system to be partitioned. *Id.* at 1284. The Federal Circuit found no disclaimer of non-partitioned memory, because systems could practice the patent even if only some of their memory was partitioned. *Id.* at 1290. In *Sandisk*, the Federal Circuit stressed that the patentee's statements describing partitioning requirements of the patented memory system did not exclude the possibility that other, non-patented memory may exist in the same system. *Id.* Likewise, while U Penn's statements about the '752 Patent invention exclude ADCC or CDC from the patented method (which is limited to down regulation), they do not indicate that no ADCC or CDC can ever occur when the claimed antibody is administered.

U Penn also cites additional portions of the prosecution history to show that both it and the PTO recognized that ADCC/CDC could occur with administration of the claimed antibodies. In 1999, U Penn submitted another one of the inventors' patents, U.S. Patent Number 5,824,311, which states that anti-p185 antibodies can kill tumor cells *in vitro*. Feb. 18, 1999 Greene Decl., Ex. E. In addition, U Penn submitted information about Genentech's accused Herceptin product as evidence of enablement. This information stated that Herceptin mediates ADCC and preferentially kills cells overexpressing p185. Feb. 18, 1999 Greene Decl., Ex. G. As U Penn argues, these references indicate that the inventors were at least aware that the claimed antibodies could cause ADCC/CDC. These references support U Penn's argument that its statement was not intended to state otherwise.

Genentech argues that U Penn's statements were a clear disclaimer. Genentech cites *Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375-76 (Fed. Cir. 2008). In this case, the patentee distinguished the prior art by stating that the claimed invention did not require "a built-in display or keyboard" (such as a laptop would have). *Id*. The patentee also argued that "[f]or the same sized unit as a conventional lap-top computer, the invention does require that peripherals be made available at each location." *Id*. at 1377. Because the patentee had clearly distinguished the claimed invention from prior art systems with built-in displays and keyboards, the

Federal Circuit found that these elements were properly excluded from the claim scope. *Id.* at 1379. U Penn argues that the disclaimer in *Computer Docking* is different from the asserted disclaimer here, because a computer cannot both have and not have a portable display and keyboard, while the claimed antibodies can downregulate without using ADCC/CDC even though they might otherwise trigger ADCC/CDC. Genentech also relies on *Plant Genetic Sys. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1345 (Fed. Cir. 2003). Here, the examiner rejected the claims to transformed plants as non-enabled, because "there [was] no evidence that fertile transgenic plants [could] be regenerated in most agronomic monocots, as in the case of maize or rice." *Plant Genetic Sys.*, 315 F.3d at 1345. To overcome this objection, the patentee added the limitation of plants "susceptible to infection and transformation by Agrobacterium and capable of regeneration." Because monocots were not susceptible to transformation at the time, this amendment disclaimed monocot plants from the claim scope. *Id*. As with the *Computer Docking* systems, a plant cannot be a monocot and a dicot at the same time. As a result, the inferences drawn from the prosecution histories in *Computer Docking* and *Plant Genetic Systems* are not transferable to this case. The Court finds that *Sandisk* is the more analogous case, and concludes that there was no clear disclaimer.

If the Court adopted the negative limitation Genentech proposes, it would mean that any use of the claimed antibodies which resulted in down regulation as well as ADCC/CDC is non-infringing. But U Penn's statement about ADCC/CDC should not have led the public to expect this. In *Sandisk*, the Federal Circuit noted that "an ambiguous disclaimer . . . does not advance the patent's notice function or justify public reliance." *Sandisk*, 415 F.3d at 1287. The Court finds that while the disclaimer here prohibits U Penn from claiming ADCC/CDC as an element of the patented method, it does not justify reliance on the idea that any method resulting in both down regulation and ADCC/CDC is non-infringing.

2. preventing or eliminating metastasis

Genentech argues that U Penn disclaimed prevention or elimination of metastasis while distinguishing the Yu reference. Specifically, U Penn distinguished this reference by arguing that it was "specifically directed at preventing metastasis of tumors," but that "metastasis of tumors and

transformation of normal cells to tumor cells are totally and completely different events." Opp'n at 24. This statement simply distinguishes Yu by noting that the Yu method acts on cells that are already cancerous, while the patented invention works on cells before they have become cancerous. It does not say that the patented invention cannot prevent metastasis. Because preventing a cell from becoming cancerous necessarily prevents it from gaining the ability to metastasize, there is no reason to read the cited language as a "clear and unmistakable" disclaimer of preventing metastasis. To do so would contradict the plain meaning of the claims. Therefore, the Court does not find that the patentees disclaimed "preventing or eliminating metastasis," and does not read this as a limitation of the claims.

3. enhancing chemotherapy

Genentech argues that U Penn disclaimed "enhancing chemotherapy" when it distinguished the Hellstrom and Kim references. The examiner had rejected the claims based on these references, finding that they suggest the combination of antibody treatment and chemotherapy. The examiner noted Hellstrom's teaching that "antibody therapy remedies the unresponsiveness of the patients to chemotherapy, and results in complete remission." The examiner further noted that Kim taught prevention or delay of the recurrence of "advanced gastric cancer." In Kim, surgery is followed by early postoperative immunotherapy and chemotherapy, and the combination therapy is more effective than surgery alone or surgery followed only by chemotherapy. *See* March 14, 2000 Office Action. In its response, U Penn argued that Hellstrom taught that the antibodies merely "render[ed] the cells more susceptible to chemotherapeutic killing, possibly by increasing drug uptake." Similarly, U Penn stated that Kim "teaches synergistic use with chemotherapeutics." *See* June 30, 2000 Amendment at 6-9. Genentech argues that these statements disclaimed any synergistic use of the antibodies claimed in the '752 Patent in combination with chemotherapy.

Pursuant to the guidance of *Sandisk*, discussed extensively above, the Court finds that this alleged disclaimer is too ambiguous to definitively exclude any enhancement of chemotherapy from the scope of the claims. *Sandisk*, 415 F.3d at 1287. These statements appear to distinguish the cited references as describing antibodies that would not be effective to prevent cells from becoming cancerous on their own, but only work in combination with chemotherapy. In contrast,

the patent claims antibodies that can work independently. Therefore, a reasonable interpretation of these statements is that the '752 Patent claimed invention is distinguished because its antibodies are not chemotherapy-dependent. Notably, after the Amendment with the purported disclaimer, U Penn added claims specifically drawn to combining chemotherapeutic agents with the claimed antibodies, and these claims were ultimately allowed. *See* claims 15 and 16 (claiming cis-platin, a chemotherapeutic agent). Genentech argues that these claims cover the combination of chemotherapeutic agent and antibody, but that any resulting enhancement of chemotherapy was disclaimed. However, the Court finds the cited statements too ambiguous to effect such a disclaimer.

The Court does not agree with Genentech regarding the alleged disclaimers. Accordingly, in light of the constructions of "down regulation" and "breast cancer cells," the Court finds that the term "inhibiting development into breast cancer" needs no further construction

F. "has the complementarity determining regions"/"has the variable regions" and "with complementarity determining regions"/ "with variable regions"

Because these claim terms are lengthy, the Court inserts a chart to show the terms and the parties' constructions.

Claim Terms	U Penn Proposed Construction	Genentech Proposed Construction
Claim 2: "the antibody has the complementarity determining regions from an antibody" produced by a cell line ATCC Deposit No. HB10493	"the antibody has all of the complementarity determining regions of expressed antibody 7.16.4. Complementarity determining regions are the hypervariable regions of the antibody."	"the antibody has the same amino acid sequences as found in each of the hypervariable regions of the heavy and light chains of the 7.16.4 antibody."
Claim 3: "the antibody has the variable regions from an antibody produced by a cell line ATCC Deposit No. HB10493"	"the antibody has all of the variable regions of expressed antibody 7.16.4. Variable regions are comprised of complementarity determining regions and framework regions."	"the antibody has the same amino acid sequences as found in the approximately 110-115 amino acids located at the N-terminus of the heavy and light chains of the 7.16.4 antibody."
Claim 6: "antibody with complementarity determining regions from the antibody produced by ATCC Deposit No. HB10493"	"the antibody has hypervariable region(s) of expressed antibody 7.16.4. The claim does not require the presence of all the hypervariable regions of antibody 7.16.4."	"the antibody has the same amino acid sequences as found in each of the hypervariable regions of the heavy and light chains of the 7.16.4 antibody."

Claim 7: "antibody with variable regions from the antibody produced by ATCC Deposit No. HB10493"	"the antibody has variable region(s) of expressed antibody 7.16.4. The claim does not require the presence of all the variable regions of antibody 7.16.4. Variable regions are comprised of complementarity determining regions and framework regions."	"the antibody has the same amino acid sequences as found in the approximately 110-115 amino acids located at the N terminus of the heavy and light chains of the 7.16.4 antibody."

A short introduction to some of the terms at issue is required. Antibodies are proteins that can bind to specific target molecules, called antigens. Antibodies are made up of heavy and light protein "chains." An antibody's ability to bind is determined by its structure, and specifically by areas of the heavy and light chains called variable regions (VRs). VRs are sub-divided into complementarity-determining regions (CDRs) and framework regions (FRs). CDRs (which are sometimes called hypervariable regions) are the parts of the antibody that actually interact with an antigen. FRs are adjacent to CDRs. Together, FRs and CDRs make up the VR. The VR is made up of the 110 – 115 amino acids at one end (the "amino" or "N terminal") of the heavy or light chains. *See* Cote Decl. ¶ 116.

Regarding claims 2 and 3, the parties appear to agree that these claims require complete identity at the amino-acid level between the CDRs (claim 2) and VRs (claim 3) of antibody 7.16.4. U Penn did not argue against adoption of Genentech's proposed construction of claims 2 and 3 in its Opening Brief or its Reply Brief. In addition, Dr. Schlissel stated in his declaration that these claims require complete amino-acid identity. *See* Corrected Schlissel Decl. ¶ 176 ("A person of ordinary skill in the art would understand these claims as requiring respectively all the CDRs or the variable regions of the 7.16.4 antibody to be present in the claimed antibody . . . claims 2 and 3 . . . require that the claimed antibody have *all the precise amino acid sequences of the variable regions and CDRs* from the [7.16.4] antibody). Although U Penn appeared to back away from this at the claim construction hearing by arguing that the proper focus for construing claims 2 and 3 should be on the three-dimensional structure of antibodies rather than on amino acid sequences, Dr. Schlissel's unambiguous statement confirms the understanding of persons skilled in the art that amino acid sequence determines the "final structure" of a protein. *See* Corrected Schlissel Decl. ¶

158. Thus, the Court finds that there is no real dispute between the parties as to the meaning of claims 2 and 3.

Regarding claims 6 and 7, the parties dispute the level of similarity required between the claimed humanized antibody and the 7.16.4 mouse antibody. U Penn argues that because humanized antibodies are the subject of claims 6 and 7, a person having skill in the art would understand that complete, amino-acid identity is not required by these claims. This is because the 7.16.4 antibody is a mouse antibody. The process of "humanizing" antibodies requires removing most of the non-human amino acid sequences, because these sequences can cause unintended immune reactions when introduced in a human. *See generally* Corrected Schlissel Decl. ¶¶ 155-169. However, some portion of the VRs or CDRs from the mouse antibody must be maintained in order for the antibody to keep its ability to bind its specific antigen (in this case, p185). *Id*. U Penn argues that because claims 6 and 7 address humanized antibodies, and because researchers making humanized antibodies focus on the three-dimensional structure of the molecules rather than on perfect amino-acid identity, these claims should not be limited to require *all* the amino acid sequences from *all* the VRs and CDRs of 7.16.4. U Penn also argues that because claims 6 and 7 do not recite "the . . . regions" but only "regions," by the principle of claim differentiation, they should mean something different from claims 2 and 3.

Genentech responds that the use of "regions" in claims 6 and 7 requires a plural number of regions. Genentech also cites the prosecution history, in which U Penn argued that "the humanized antibody of the claimed invention retains the non-human antigen binding site (entire variable regions or particular CDRs . . .) within a framework." June 30, 2000 Response and Amendment at 4. The Court agrees with U Penn that the cited prosecution history language does not dictate that claims 6 and 7 must claim multiple VRs/CDRs. As U Penn points out, in patent claims "[t]he plural can describe a universe ranging from one to some higher number, rather than requiring more than one item." *Versa v. Ag-Bag*, 392 F.3d 1325, 1330 (Fed. Cir. 2004). In light of the fact that claims 2 and 3 claim "the" regions, while claims 6 and 7 claim only "regions," the Court finds that claims 6 and 7 require only one of the relevant regions. However, the Court is not persuaded by U Penn's argument that the word "regions," which Dr. Schlissel admits requires amino-acid identity

in the context of claims 2 and 3, suddenly changes to refer to three-dimensional structure simply because claims 6 and 7 address "humanized" antibodies. While omission of the word "the" means that only one region must share amino-acid identity with 7.16.4, the patent does not support changing the meaning of "region" based on the fact that claims 6 and 7 relate to humanized antibodies.

Accordingly, the Court adopts Genentech's constructions regarding claims 2 and 3. The Court construes the relevant language from claim 6 to mean "**the antibody has the same amino acid sequences as found in at least one of the hypervariable regions of the heavy and light chains of the 7.16.4 antibody**" and construes the relevant language from claim 7 to mean "**the antibody has the same amino acid sequences as found in the approximately 110-115 amino acids located at the N terminus of at least one of the heavy or light chains of the 7.16.4 antibody.**"

IT IS SO ORDERED.

Dated: May 9, 2011

LUCY H. KOH
United States District Judge